A pilot study evaluating the effect of 2D antiscatter grids on CBCT image quality

Protocol Number: 20-1684

National Clinical Trial (NCT) Number: NCT04565457

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PROTOCOL AMENDMENT HISTORY

Version	Date	Description of Change	Brief Rationale
v01AUG2022	01AUG2022	Updated NCT #; modified description for storage of device	Clarified 2D grid prototypes will be placed in an enclosure when stored in the locked storage cabinet and during transport from storage to the linac vault to ensure no damage occurs to the grids.
v12MAY2023	12MAY2023	Added "prostate bed" to inclusion criteria, clarified that SOC CBCT scans may be performed prior to the research	Updated information to include a broader scope of participants, allow for multiple anatomical regions since this is a pilot study, and to allow for

Version	Date	Description of Change	Brief Rationale
		CBCT scans occurring, clarified that non-contrast or contrast-enhanced MDCT scans are optional and that either scan can be performed, clarified Groups 1-4, updated UADE reporting information	more flexibility with consenting participants.
v12JAN2024	12JAN2024	Modification of endpoints, clarification to exclusion criterion regarding WOCBP, additional two participants (n=42)	The modification of endpoints will allow for important qualitative and quantitative analyses which will provide more information when reporting results.
v15NOV2024	15NOV2024	Updated primary endpoint, Modified protocol for proton therapy	The modification allows for use of image quality metrics to quantify tissue visualization, rather than the observer drawn contours which is a labor-intensive approach. For the proton therapy cohort: we will do two research scans (instead of one). One scan is with the 2D grid, and the other is without the 2D grid.

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STATEMENT OF COMPLIANCE

This is an investigator-initiated study. The Principal Investigator (PI), Cem Altunbas, PhD, is conducting the study and acting as the sponsor. As the Sponsor-Investigator, both the legal/ethical obligations of a PI and those of a Sponsor will be followed.

The trial will be carried out in accordance with Good Clinical Practice (GCP) as required by applicable United States (US) laws and applications, including but not limited to United States (US) Code of Federal Regulations (CFR) applicable to clinical studies (45 CFR Part 46, 21 CFR Part 50, 21 CFR Part 56, and/or 21 CFR Part 812), as applicable.

The PI will assure that no changes to the protocol will take place without documented approval from the Institutional Review Board (IRB). All personnel involved in the conduct of this study have completed Human Subjects Protection Training.

I agree to ensure that all staff members involved in the conduct of this study are informed about their obligations in meeting the above commitments.

Sponsor-Principal Investigator: Cem Altunbas, PhD
Print/Type Name

Signature: _____ **Date:** _____

Site Principal Investigator: _____
Print/Type Name

Signature: _____ **Date:** _____

LIST OF ABBREVIATIONS

CBCT	Cone beam computed tomography
CCC	Concordance correlation coefficient
cGy	Centigray
CI	Conformity Index
CT	Computed tomography
DIR	Deformable image registration
Gy	Gray
HD	Hausdorff distance
ICC	Intra-class correlation coefficient
MDCT	Multi-detector CT. This is simulation CT scanner akin to diagnostic CT scanners
SOC	Standard of Care
UADE	Unanticipated Adverse Device Effect
UFHPTI	University of Florida Health Proton Therapy Institute
WOCBP	Women of Child-bearing Potential

1 PROTOCOL SUMMARY

1.1 SYNOPSIS

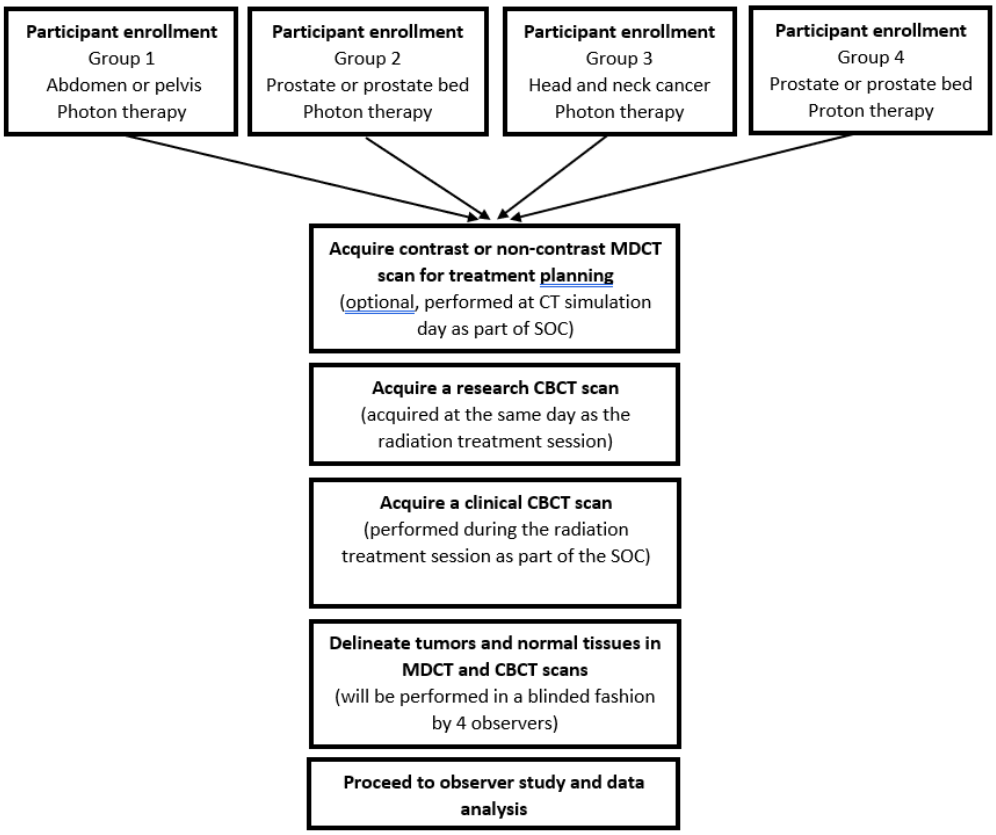
Protocol Title:	*A pilot study evaluating the effect of 2D antiscatter grids on CBCT image quality*
Objectives:	• ***Primary Objective:*** *To assess the improvement in tissue visualization in CBCT images.* • ***Secondary Objective:*** *To evaluate the accuracy of tissue delineation in CBCT images by auto-segmentation software.* • ***Tertiary Objective:*** *To assess the utility of CBCT images in qualitative and quantitative imaging tasks*
Endpoint:	• ***Primary Endpoint:*** *Improvement in image quality and quantitative accuracy as measured by established objective image quality metrics.* • ***Secondary Endpoints:*** *Similarity of anatomical structures delineated by auto-segmentation software and expert observers, as measured by established similarity metrics.* • ***Tertiary/ exploratory:*** *Improvement in qualitative and quantitative imaging tasks as measured by quality metrics pertinent to each task.*
Population:	• ***Sample size*** ○ *Maximum number of participants that can be enrolled is 50 to allow for screen failures or withdrawn patients that are not evaluable. Minimum number of participants to be enrolled is 42.*
Phase:	*Pilot*
Participating Sites:	*1. University of Colorado Anschutz Medical Campus, Aurora, CO* *2. University of Florida Health Proton Therapy Institute, Jacksonville, FL*
Description of Study Intervention:	*For photon therapy cohort, one CBCT scan will be acquired for each participant using the 2D grid technology, For the proton therapy cohort, two CBCT scans will be acquired for each participant; one*

with the 2D grid technology, the other one without the 2D grid technology.

Study Duration: *4 years*

Participant Duration: *Up to four months from the time of screening to completion of imaging session #2. The total time spent by the participant will be approximately 30 minutes, and the intervention will be performed on the day of participant's radiation treatment.*

1.2 STUDY SCHEMA



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1.3 SCHEDULE OF EVENTS

Schedule of events for participants in Photon Therapy cohort			
Procedures / Assessments	**Screening**	**Imaging session # 1**	**Imaging session #2 (end of study)**
	Days –28 to 1	**Day 1**	**Days 2-90**
Informed Consent and HIPAA Authorization[1]	X[1]	X[1]	X[1]
Inclusion/Exclusion[1]	X[1]	X[1]	X[1]
Pregnancy Test for WOCBP (SOC)		X	
Optional non-contrast or contrast MDCT scan (both scans are SOC)[2]		X	
Research CBCT scan with 2D grid (The only intervention during the clinical trial)			X[3]
Clinical CBCT scan (SOC)			X[3]

Schedule of events for participants in Proton Therapy cohort			
Procedures / Assessments	**Screening**	**Imaging session # 1**	**Imaging session #2 (end of study)**
	Days –28 to 1	**Day 1**	**Days 2-90**
Informed Consent and HIPAA Authorization[1]	X[1]	X[1]	X[1]
Inclusion/Exclusion[1]	X[1]	X[1]	X[1]
Optional non-contrast or contrast MDCT scan (both scans are SOC)[2]		X	
Research CBCT scan with 2D grid			X[4]
Research CBCT scan without 2D grid[5]			X[4]

[1]A participant can be consented (and eligibility determined) either before or after the start of their treatment. A research scan (and SOC CBCT scan) can be performed either on the same day or another day after the consent is signed.
[2]Optional collection of either non-contrast or contrast-enhanced MDCT scans.
[3]Clinical and Research CBCT scans can be performed in either order on the same day.
[4]Research CBCT scans with and without 2D grid in the Proton Therapy cohort can be performed in either order on the same day.
[5]Research CBCT scan without 2D grid in the Proton Therapy cohort is equivalent to a standard clinical CBCT scan.

2 INTRODUCTION

2.1 STUDY RATIONALE

Introduction:
As radiation therapy is delivered in multiple sessions, often spanning weeks, both the shape and location of normal tissues and tumors may change throughout the course of treatment. If such geometric changes are not accounted for, they may lead to under-dosage to tumors or increased dose to normal tissues, potentially reducing tumor control and increasing toxicity. To monitor geometric changes and account for them in treatment plans (when needed), 3D images acquired during radiation delivery sessions can be utilized.

While cone beam computed tomography (CBCT) is the most frequently used 3D image guidance modality in radiation therapy, its role in monitoring and accounting for geometric changes in tissues has been limited due to CBCT's poor image quality. Clinicians may not clearly visualize tumors and surrounding anatomy to assess changes, and CT numbers are inaccurate to conduct CBCT-based dose calculations, which are essential for assessing radiation dose coverage of targets during radiation delivery.

Scattered radiation is one of leading causes of degraded image quality in CBCT. To address this problem, we developed a novel device, referred to as 2D antiscatter grid, which reduces scatter intensity in CBCT acquisitions. 2D grid is composed of a 2D array radiopaque septa focused to the x-ray source, which transmits primary, or useful x-rays, and absorbs vast majority of scattered x-ray due to their broad angle of incidence on the grid. To date numerous 2D grid prototypes have been developed (Fig. 1), and the improvement in image quality was validated in phantom-based imaging experiments [1-5]. Example CBCT images acquired with today's radiographic grids and the 2D grid technology are shown in Fig. 2. However, clinical efficacy of 2D grid technology cannot be evaluated in phantoms, as the appearance of human anatomy cannot be fully emulated, and the effect of improved image quality on clinical decision making cannot be assessed.

Hence, in this Pilot, our goal is to evaluate the clinical efficacy of 2D grids in improving CBCT image quality for patients treated with radiation therapy. When the image quality is improved at a clinically significant level, we hypothesize that organ boundaries and tumors will be visualized better, a key task for target localization and treatment monitoring in CBCT-guided treatment delivery. Moreover, we hypothesize that image intensity and texture features will be more consistent, which is essential for accurate dose calculations and assessment of changes in tissues throughout the radiation therapy course.

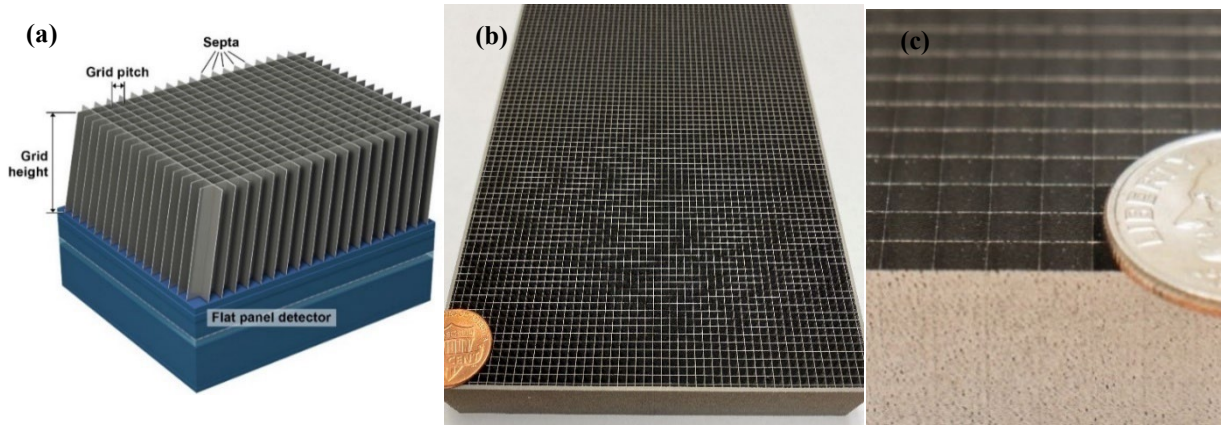


Fig. 1. (a) 2D antiscatter grid is a 2D array of through-holes separated by tungsten septa, directly attached to the protective cover of the flat panel detector. To account for x-ray divergence in cone beam geometry, each grid wall, or septum, is uniquely aligned toward the x-ray source to minimize the shadow of the 2D grid on the detector. (b), Fabricated 2D antiscatter grid. (c), Close-up photo of the grid.

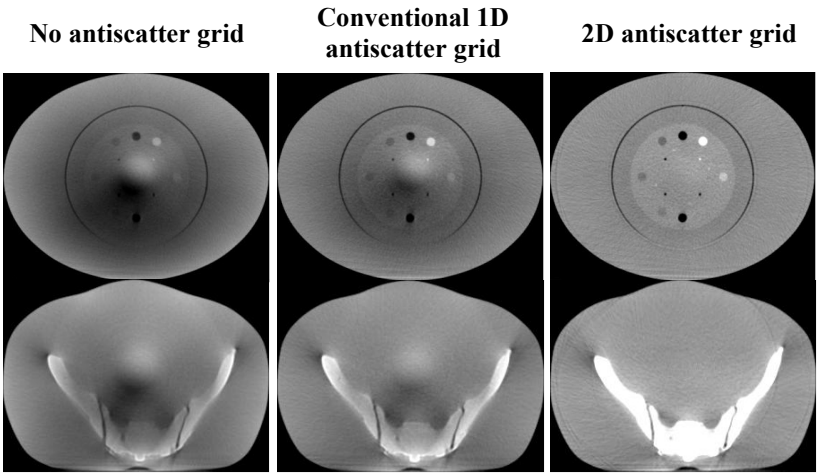


Fig. 2. Effect of antiscatter grids on CBCT image quality in pelvis sized phantoms

No scatter mitigation: Soft tissue visualization is corrupted. Severe, dark shading artifacts are visible.

Conventional 1D antiscatter grid: While image artifacts are reduced, the image quality is still poor. This is the antiscatter grid used in Varian TrueBeam CBCT system.

2D antiscatter grid technology to be evaluated in the clinical trial: Shading artifacts are suppressed, and low contrast objects are clearly visible.

Objectives:

To test the hypotheses above, our first objective is to evaluate whether tissue visualization and quantitative accuracy is improved in CBCT images acquired with the 2D grid. These evaluations will be performed by analyzing objective image quality metrics, such as absolute CT number error and contrast to noise ratio.

Our second objective is to evaluate whether automated anatomy segmentation software tools can segment, or delineate, anatomical structures more consistently in CBCT images acquired with the 2D grid. Since up to forty CBCT scans are generated throughout the treatment course of a patient, evaluation of geometric changes of anatomical structures may require significant clinical resources. Therefore, automation of tissue segmentation in CBCT images is essential to reduce the workload on personnel. To that end, extensive research has been done on tools for treatment monitoring automation, such as deformable image registration and automated structure delineation algorithms. However, such tools do not function well due to inaccurate CT numbers and the low-contrast resolution of CBCT.

The third and exploratory objective of this study is to evaluate the utility of CBCT images in a range of qualitative and quantitative imaging tasks. CBCT images are used or can be potentially used in a variety of tasks in radiation therapy, such as extraction of radiomics features to predict treatment response, target localization before treatment delivery, and CBCT based dose calculations. Thus, the utility of improved CBCT image quality will be explored in several different tasks. The investigations below are identified and selected tentatively by the study PI. After the completion of the research CBCT scans of study participants, the PI will consult with the study team to identify one or more exploratory objectives and proceed with the analyses. These tentative exploratory analyses are: 1) It is hypothesized that clinicians can more consistently delineate anatomy in CBCT images acquired with the 2D grid. An observer study will be conducted to evaluate tissue visualization performance in CBCT images. 2) Consistency of CBCT image intensity and texture features (also known as radiomics features) will be analyzed. CBCT radiomics features can be used as biomarkers to assess treatment response and toxicity. However, the accuracy of such approaches has been hampered by the poor consistency of radiomics features in CBCT images. The exploratory analysis in this study will evaluate whether consistency of radiomics features can be improved by using the proposed CBCT scans. 3) Image quality improvement in research CBCT scans will be analyzed qualitatively in an observer study. Both research and standard clinical CBCT scans will be ranked by observers based on the perceived image quality. This qualitative, or subjective, image quality analysis will complement our quantitative image quality analysis. 4) Image quality in research and standard clinical CBCT scans will be analyzed using quantitative and objective image quality metrics, such as contrast to noise ratio and CT number accuracy. We hypothesize that we will observe a statistically significant difference between the image quality metrics extracted from research and standard clinical CBCT

scans. 5) CBCT images can be used for dose calculations during radiation treatment sessions. Poor CBCT image quality can adversely affect CBCT-based dose calculation accuracy. Hence, research and standard clinical CBCT scans will be used for dose calculations, and dose calculated in CBCT images will be compared to the dose calculated in gold standard MDCT images. Dose volume histograms will be used to calculate the dosimetric errors between CBCT and MDCT based dose calculations. We hypothesize that the proposed research CBCT scans will reduce the dosimetric errors.

Study intervention:
In the photon therapy cohort, each study participant will receive one additional CBCT scan, with 2D antiscatter grid in place. This is the only intervention in the study, referred as research CBCT scan, and it will be performed on one of the days during the participant's radiation treatment course. This additional research CBCT scan will be used strictly for the objectives of this study. It will *not* be used as part of standard clinical care, such as imaging guidance of participant's radiation treatment or diagnostic purposes. To deliver participant's radiation treatment under CBCT guidance, a standard clinical CBCT scan will be acquired, as in standard clinical care protocols.

In the proton therapy cohort, each study participant will receive two additional CBCT scans, one with and the other without 2D antiscatter grid in place. The CBCT scan without 2D antiscatter grid will be equivalent to the standard clinical CBCT scan available in the proton therapy CBCT system. As in the photon therapy cohort, these images will not be used as part of standard clinical care. The participant's radiation treatment will be delivered by using the standard of care image guidance protocols in proton therapy.
The participant's involvement with the study will end with the completion of the study intervention. There will not be follow-up visits. Each participant's standard clinical CBCT scan will serve as the control. This way, image quality of research CBCT scans with 2D grid will be evaluated with respect to standard clinical CBCT scans. For each participant, imaging dose and technical parameters of the research CBCT scan will be identical to the standard clinical CBCT scan, and the two scans will be performed on the same day in either order.

Study population:
A total of 42 participants will be enrolled in this study. They will receive CBCT-guided photon or proton therapy.

CBCT image quality depends on patient specific factors, such as the anatomical site of interest and patient size. Thus, 32 participants will be accrued from patients who receive radiation therapy for prostate and prostate bed (11 patients), and other cancers, which include abdomen, head and neck, or cancers in the pelvis region (21 total patients). These participants will be selected from a patient population treated with megavoltage photon therapy.

CBCT image quality also depends on the CBCT system characteristics. Due to major differences in gantries used for photon and proton therapy systems [6, 7], the impact of 2D grid on CBCT image quality may be different in photon and proton therapy. Therefore, 10 prostate and prostatebed cancer patients, who are treated with proton therapy, will also be accrued.

2.2 BACKGROUND

In preliminary studies, we showed that CBCT images acquired with 2D grid can substantially improve image quality and dose calculation accuracy. Below is the summary of our findings.

The evaluation of 2D antiscatter grids in phantom (objects that mimic human anatomy) imaging experiments: We developed numerous 2D grid prototypes, installed them in a clinical CBCT system, and evaluated their effect on image quality in phantom experiments [1, 2, 5, 8, 9]. A significant improvement in image quality was observed, as summarized below.

- We observed that 2D grids can improve contrast-to-noise ratio (CNR) by a factor of two in pelvis sized phantoms, when compared to CBCT images acquired without a 2D grid. Improvement in CNR implies that soft tissue visualization can be improved, which is essential for monitoring shape and location changes of tissues throughout the course of radiation treatment.
- Hounsfield Unit (HU) accuracy of soft-tissue like structures was in the in the order 20 HU, and image artifacts were significantly reduced when compared to CBCT images acquired without a 2D grid. These results also indicate that image intensity and texture features (radiomics features) can be more consistent and reproducible in CBCT images acquired with a 2D grid.

Accuracy of radiation dose calculations using CBCT images acquired with a 2D grid: We observed that dose calculation errors in CBCT images acquired with 2D grid are within 2-3%, when compared to dose calculations in gold standard MDCT images [4]. These results indicate that CBCT-based dose calculations may be feasible for CBCT-based treatment plan modifications.

2.3 RISK/BENEFIT ASSESSMENT

2.3.1 KNOWN POTENTIAL RISKS

The 2D antiscatter grid device does not pose any significant risks to study participants. This is because the:

a) CBCT images acquired with 2D grid will not be used for any diagnostic purposes or as part of the standard clinical care received by the participant, such image guidance of radiation treatment. CBCT images acquired with the 2D grid will be used strictly to achieve the research goals of this study, which do not interfere with participants' standard clinical care.
b) 2D grid is not an implanted device; it is installed in the CBCT imaging system, and the participant does not have any physical interaction with the device. The grid is made from tungsten (see Fig. 1) and aluminum parts in solid form. The enclosure for the grid will be fabricated from carbon fiber and metal support structures in solid form. These components do not emit any fumes, dust, electromagnetic waves, or electrical current, and therefore they do not present a potential for serious risk to the health, safety, or welfare of the participants.
c) CBCT imaging system and 2D grid used in the study intervention, are not purported, or represented to be for a use in supporting or sustaining human life.
d) 2D grid is not a single use device; the same 2D grid will be used during research CBCT scans of multiple participants. The 2D grid and its enclosure are not in contact with the participant, and they do not pose a biological hazard. Sterilization or high-level disinfection is not required. Before and after each use, grid assembly will be cleaned using standard hospital procedures, such as wiping the assembly with disinfecting wipes.
e) Components of the 2D grid assembly do not change form or emit any hazardous media due to x-ray radiation during a CBCT scan. Thus, the use of 2D grid and its components do not pose a health or safety hazard when used in the presence of radiation emitted by the CBCT imaging system. It should be noted that 2D grid assembly will be removed during therapeutic radiation delivery to the participant, as part of the standard clinical care.

Potential risks below are considered minor or insignificant risks:

1) Long range risks: Participant will receive additional imaging dose due to one additional CBCT scan with 2D grid in the photon therapy cohort and two additional CBCT scans in the proton therapy cohort. Organ doses will be in the range of 0.5-3 cGy per scan in the photon therapy cohort and 1-1.5 cGy per scan in the proton therapy cohort [10]. In the context of radiation therapy, this is a very low level of radiation dose, and excess cancers have not been observed, or detectable, due to such a small increase in dose given to radiation therapy patients [11, 12].

While observed data does not exist, Dzierma et al. developed a model for excess cancer risk in pediatric radiation therapy patients due to CBCT scans [13]. They estimated that excess cancer risk is less than 0.2 cases per 10,000 person-years for 11 daily CBCT scans performed during radiation therapy. In our clinical trial, the excess risk due to research CBCT scan is expected to be significantly lower than Dzierma et al.'s estimate, since only one additional CBCT scan will be performed (as opposed to 11), and only adult patients will be accrued in our study, who have lower risk of secondary cancers due to radiation exposure [11, 14].

2) Immediate risks: While mechanical breakdown of the 2D grid has not happened during our experiments, there is a small chance that the 2D grid may break during a patient scan. To prevent the risk of bodily injury due to falling debris, grid prototypes will be checked for mechanical integrity before each scan, and a carbon-fiber protective enclosure will be placed on the grid during the scans.

2.3.2 KNOWN POTENTIAL BENEFITS

- **To Participant:** The geometric changes in targets and normal tissues may not be quantified accurately using standard clinical CBCT scans and standard clinical CBCT image evaluation protocols. Whereas, in the research CBCT scan, we hypothesize normal tissues and targets will be better visualized and will be delineated. With the help of accurate tissue delineations, changes in tissue shape and locations will be quantified, with respect to the delineations in the treatment planning CT scan (also known as simulation CT scan). If geometric changes are deemed significant by the radiation oncologist, participant's treatment plan may be modified to assure intended dose distribution, which can potentially improve tumor control and reduce treatment toxicity.
- **To Society:** With improved image quality in CBCT images:

1) Personalized treatment monitoring and modifications throughout the treatment course can be enabled by using widely available radiation therapy systems equipped with CBCT. CBCT images acquired during treatment sessions will be utilized to modify treatment plans (when needed), to assure the intended dose coverage of tumors and sparing of normal tissues throughout the treatment course. Potential clinical benefits of this approach have been reported for numerous disease sites, including the liver [15], pancreas [15-17], head & neck [18-22], bladder [23], cervix [24-26], and thorax [27]. This approach may also allow therapeutic dose escalation, further improving treatment outcomes.

While not all patients will benefit from such treatment modifications, improved CBCT image quality is still important to identify patients who are likely to benefit from this approach.

2) Serially acquired high-quality CBCT images can be utilized as biomarkers to predict treatment response and toxicity [28, 29]. However, these methods are challenging to implement clinically due to low quality of CBCT images.

2.3.3 ASSESSMENT OF POTENTIAL BENEFITS

The risks to participants are reasonable in relation to the anticipated benefits to participants and/or society, and in relation to the importance of the knowledge that may reasonably be expected to result, thereby falling in favor of performing the study:

Risk-benefit assessment for the participant: The participant may benefit from evaluation of target dose coverage and dose sparing of normal tissues with the research CBCT scan. The radiation dose via the research CBCT scan to the patient is considered very small in the context of radiation therapy, as described below.

Patients enrolled in our study will receive radiation doses in the 30-78 Gy range at the target, and a minimum of 2-3 Gy will be given to normal tissues surrounding the targets. In addition, patients will be imaged 5 to 40 times using CBCT or 2D radiographs throughout their radiation therapy course, as part of their standard clinical care. Hence, one research CBCT scan in the photon therapy cohort and two research CBCT scans in the proton therapy cohort will increase the total delivered dose to the study participant by 0.2% to 1%.

Risk-benefit assessment for society: Once clinically implemented, 2D grid technology will improve CBCT image quality, and enable CBCT-based treatment monitoring and modifications. 2D grid will not introduce any added risks. CBCT imaging dose and other CBCT scan parameters will remain as in today's standard clinical CBCT scans.

The importance of the knowledge gained: Clinically significant improvement in CBCT image quality, and its clinical efficacy, cannot be evaluated in phantoms or in simulations. Thus, this study is crucial to quantify the improvement in tissue visualization and determine whether the quantitative accuracy in CBCT images (i.e. accuracy of image intensity and texture features) is comparable to gold standard MDCT images.

3 OBJECTIVES AND ENDPOINTS

OBJECTIVES	ENDPOINTS	JUSTIFICATION FOR ENDPOINTS
Primary: To assess the improvement in tissue visualization in CBCT images	Improvement in image quality and quantitative accuracy as measured by established objective image quality metrics.	We will evaluate absolute CT number error, image artifact amplitude, and contrast to noise ratio, which are metrics that quantify the image quality. We hypothesize that values of these metrics will be improved in CBCT images acquired with the 2D grid.
Secondary: To evaluate the accuracy of tissue delineation in CBCT images by auto-segmentation software.	Similarity of anatomical structures delineated by auto-segmentation software and expert observers, as measured by established similarity metrics.	Auto-segmentation software is a highly desired tool that is expected to generate delineations similar to delineations by human observers. We will use delineations by observers as the gold standard. We will measure the similarity between the auto-segmented delineations and observer delineations.
Tertiary/exploratory: To assess the utility of CBCT images in qualitative and quantitative imaging tasks	Improvement in qualitative and quantitative imaging tasks as measured by quality metrics pertinent to each task	CBCT images are used in a wide variety of tasks. Some task examples are tissue delineation for treatment adaptations, radiomics feature evaluation, radiotherapy dose calculations, and target localization. Thus, image quality metrics will be identified for each task, and the utility of CBCT images in each task will be evaluated using the quality metrics associated with each task.

4 STUDY DESIGN

4.1 OVERALL DESIGN

This is a Pilot study that investigates the CBCT image quality improvement provided by the 2D antiscatter grid technology. The primary objective is to assess the improvement in tissue visualization and CT number accuracy, as measured by objective image quality metrics.

- This is a single arm study, where all participants will be scanned with a CBCT system equipped with 2D antiscatter grid technology, referred to as research CBCT with 2D grid. Each participant will also be scanned with a standard clinical CBCT, which will serve as the baseline, or control. Thus, the image quality improvement in research CBCT with 2D grid will be assessed with respect to standard clinical CBCT without 2D grid.
- We anticipate enrolling a total of 42 participants. Groups (1) and (3) will have, in any combination, the collective total value of 21 participants. Group (2) will have 11

participants and Group (4) will have 10 participants. The groups are described as the following:

Group (1), Photon therapy patients with treatment sites in abdomen or pelvis: It is particularly challenging to use CBCT to visualize organ boundaries in the abdomen. Disease sites in the abdomen, e.g. the pancreas and liver, are particularly likely to benefit from "online" adaptive radiation therapy due to the proximity of the gastrointestinal tract to targets (online: plan is modified while the patient is on the treatment couch using volumetric setup images).

Group (2), **Photon therapy patients with treatment sites in prostate or prostate bed:** Due to the large tissue volume in the pelvis, scatter is more pronounced, and tissue visualization is degraded. Since larger patients generate more scatter, the image quality is also patient-size dependent. Hence, we will have two subgroups; subgroup stratification will be based on the patient left-right separation at pelvis level (subgroup 1: < 40 cm, subgroup 2: ≥ 40 cm). 5 patients will be enrolled in subgroup 1 and 6 patients will be enrolled in subgroup 2. These "small" and "large' pelvis subgroups will allow evaluation of the effect of patient size on the consistency of organ delineation. The threshold of 40 cm comes from our clinical observations; CBCT images from patients with 40 cm (or more) separation are of noticeably lower quality.

Group (3), Photon therapy patients with treatment sites in head and neck: The head and neck is another region where large changes in normal tissues and tumors occur throughout the course of treatment. Thus, it will benefit from CBCT-based treatment monitoring and adaptations.

Group (4), Patients who are treated for cancers in prostate or prostate bed with Proton Therapy: Selection criteria will be same as the prostate cancer patients in Group (2); however, CBCTs will be acquired with a CBCT system designed for Proton Therapy.

The same imaging workflow will be used for all patient Groups (1)-(3), and each participant will receive one research scan. Group (4) participants will be enrolled in the University of Florida Health Proton Therapy Institute, and they will receive two research CBCT scans.

4.2 SCIENTIFIC RATIONALE FOR STUDY DESIGN

Evaluation of CBCT image quality from a clinical perspective: An essential clinical task in CBCT-guided radiation therapy is visualization of organ and tumor boundaries; clinicians often overlay MDCT images (acquired at treatment planning phase) and CBCT images (acquired at treatment delivery phase) to assess differences in tissue shapes and positions during the course of radiation therapy. Since these two image sets are acquired days or even weeks apart, geometric changes in tissue/organ boundaries between two image sets may imply under-dosing of tumors and/or over-dosing of normal tissues. In *better-quality* CBCT images, clinicians can visualize tissue boundaries more accurately and consistently.

Therefore, quality of research CBCT scans with 2D grid will be evaluated with respect to standard clinical CBCT scans without 2D grid (i.e., the control scan). Objective image quality metrics, such as absolute CT number error, artifact amplitude and contrast to noise ratio, will be extracted from each CBCT scan and the change in image quality metrics will be evaluated with

respect to the control scans. Similar studies have been performed to assess the quality of CBCT images in the context of image-guided radiation therapy [30, 31]. In addition, an observer study will be conducted, and consistency of tissue delineations by observers will be evaluated to assess the effect of CBCT image quality on tissue structure boundary visualization [32, 33].

Standard and research CBCT scans with 2D grid will be acquired on the same study participant, by using identical scan parameters. This approach addresses the following challenges associated with image quality comparisons.

- CBCT image quality depends on patient-specific factors such as patient size and shape, anatomical site of imaging study, and patient motion. By using the same patient and anatomical site for both standard and research scans, dependence of image quality on patient-specific variables is minimized.
- CBCT image quality depends on the imaging system characteristics and imaging dose. For each participant, both standard and research CBCT scans will be acquired using the same dose and scan parameters and using the same CBCT system. This approach minimizes dose and system specific effects on image quality.

4.3 JUSTIFICATION FOR DOSE

Our study quantifies the image quality improvement in research CBCT scans acquired with the 2D grid, with respect to standard clinical CBCT scans that serve as the control. All imaging parameters are kept the same for both scans. Therefore, imaging dose in research CBCT scan with 2D grid will be the same as the standard clinical CBCT scan.

4.4 END OF STUDY DEFINITION

The study will be complete after the last study participant's CBCT scans are acquired. There will not be any follow-up visits.

5 STUDY POPULATION

5.1 INCLUSION CRITERIA

In order to be eligible to participate in this study, an individual must meet all of the following criteria:

1. Provision to sign and date the consent form.
2. Stated willingness to comply with all study procedures and be available for the duration of the study.
3. Be a male or female aged 18–100.

4. Participants who will be treated or are currently being treated with CBCT-guided photon therapy for prostate or prostate-bed, abdomen head and neck, or pelvic cancers, or with image-guided proton therapy for prostate or prostate bed cancer.

5.2 EXCLUSION CRITERIA

An individual who meets any of the following criteria will be excluded from participation in this study:

1. Metallic implants in the CBCT scan volume, such as hip prostheses or spine stabilization hardware. Patients with pacemakers, defibrillators, or other implanted electronic devices. Dental implants, fillings, or fiducial markers may be acceptable, and the decision for inclusion/exclusion will be on a case-by-case basis, by reviewing prior CT images of the study candidate. Patient's prior CT images will be reviewed by the PI or the site PI.
2. Patients who do not have the ability to lie still for the duration of his/her CBCT imaging and treatment should be excluded. If image artifacts in prior scans are deemed excessive, the patient will be excluded from the study.
3. Known pregnancy. (Per SOC, a pregnancy test will be performed prior to CBCT scan on Day 1. At this time, women of child-bearing potential (WOCBP) will receive a pregnancy test to re-confirm eligibility).
    - Women of child-bearing potential are described as:
        - Age 55 or younger who have not had a negative pregnancy test within 3 days. This excludes patients who have had tubal ligation or are already post-menopausal.

5.3 LIFESTYLE CONSIDERATIONS

There are no restrictions regarding lifestyle considerations.

5.4 SCREEN FAILURES

Participant may be re-screened for eligibility with documented approval from the Sponsor-Investigator or site PI.

5.5 STRATEGIES FOR RECRUITMENT AND RETENTION

The target sample size is 42 participants. Study participants will be recruited from patients treated in the following institutions:

- Department of Radiation Oncology, University of Colorado Hospital.

- University of Florida Health Proton Therapy Institute (UFHPTI).

Both males and females that meet the eligibility criteria can participate in our study. Based on patients treated in our department last year, we expect 50% of patients offered participation to be male, and 50% to be female for the abdomen, pelvis, and head and neck cancer subgroups.

Patients from any racial or ethnic background that meet the eligibility criteria can participate in our study. Based on the patient statistics treated in our department, we expect the following ethic/racial composition: 20% of participants to be of Hispanic ethnic background, 20% of African American race, 50% of white race, and 10% to be composed of other racial or ethnic groups such as American Indian and/or Asian.

6 STUDY INTERVENTION

6.1 STUDY INTERVENTION(S) ADMINISTRATION

6.1.1 STUDY INTERVENTION DESCRIPTION

Before each intervention, the 2D grid will be installed into the CBCT system by personnel previously trained in the installation procedure. Following installation, the research CBCT scan will be acquired by radiation therapists by using the same protocol as in a standard clinical scan. It is estimated that the intervention will be completed in less than 30 minutes. Research CBCT scan can be performed either before or after study participant's radiation treatment session. Both standard clinical scan and research CBCT scan will be performed on the same day.

Two different CBCT systems will be used for the study interventions depending on the study site:

1) At University of Anschutz Medical Campus: Participants will be treated with CBCT guided photon therapy. Varian TrueBeam system (Varian Medical Systems, Palo Alto, CA) will be used for acquiring both standard clinical and research CBCT scans. TrueBeam CBCT has a standard radiographic antiscatter grid (Model name: Smit Rontgen. Manufactured by Philips, Best, Netherlands). Before acquiring the research CBCT scan (the study intervention), radiographic grid will be removed from the CBCT image receptor, and the 2D grid assembly will be installed. After research CBCT scan, 2D grid will be uninstalled and the radiographic grid will be reinstalled on the image receptor. Subsequently, the imaging system will be calibrated to bring the CBCT system back to its standard clinical configuration.

2) At UFHPTI: Participants will be treated with image-guided proton therapy. IBA Proteus system (Ion Beam Applications SA, Louvain-la-Neuve, Belgium) will be used for acquiring both standard and research CBCT scans. Before acquiring the research CBCT scan, the 2D grid assembly will be installed. After research CBCT scan, 2D grid will be

uninstalled, and the CBCT system will be brought back to its standard clinical configuration.

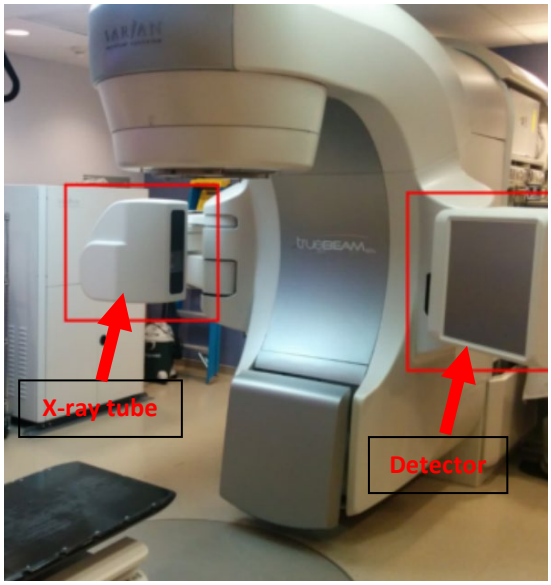
2D grid installation/deinstallation training will be conducted by the PI or other team members trained by the PI. For the Proton Therapy CBCT scans, installation procedures will be developed in collaboration with staff from UFHPTI. The role of each staff and study investigators during 2D grid installation/deinstallation procedure will be identified clearly, and their training will be documented.

2D grids prototypes are not participant-specific, but they will be designed specifically for each CBCT system at Anschutz Medical Campus and UFHPTI due to differences in CBCT system geometries. 2D grids will be assembled by PI's team at University Colorado Anschutz Medical Campus. Prototypes will be returned to the PI at the end of the study.

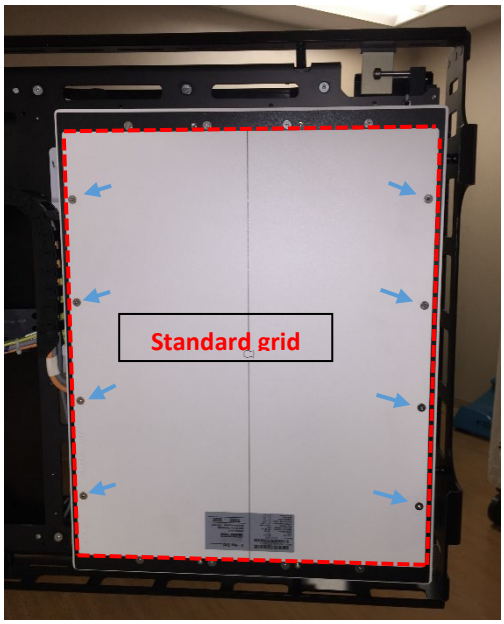
In the photon therapy cohort, the standard clinical CBCT scan, which serves as the control, will be acquired using the standard CBCT system as part of the standard clinical care. In the proton therapy cohort, the standard clinical CBCT scan will be acquired as an additional scan, it will not be part of the standard clinical care. It is important to reiterate that research CBCT scan acquired with the 2D grid will not be used in any way during participant's standard clinical care.

Cleaning, sterilization or high-level disinfection is not needed, since 2D grid assembly is not in contact with the patient.

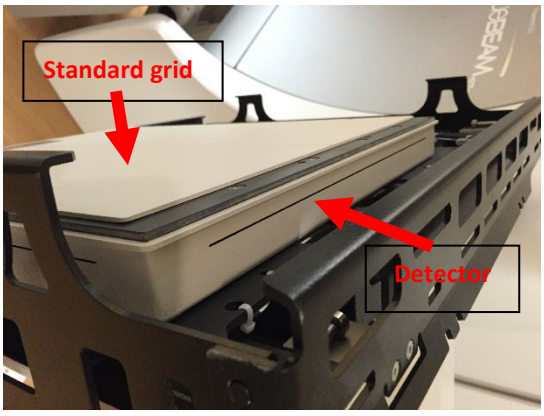
Fig. 3 Workflow for 2D antiscatter grid installation in the CBCT System



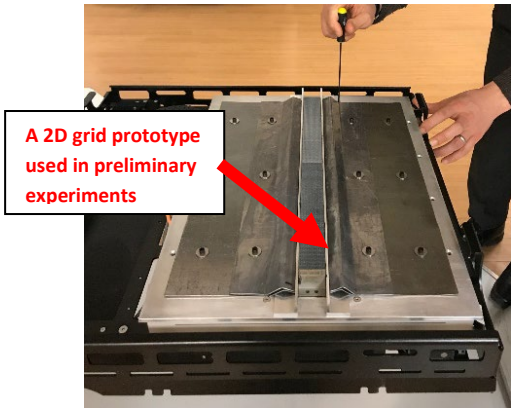
1. Components of the CBCT system. 2D antiscatter grid will be installed on the x-ray detector on the right. Detector is underneath the gray protective cover.



2. Once the protective cover is removed, the detector and the standard antiscatter grid (white plate, surrounded by red line) on the detector are accessible. Grid is fixed on the detector with 8 screws (blue arrows). For the research CBCT scan, this grid will be removed by taking the screws out.



3. The sideview of the detector and the standard antiscatter grid.



4. After removing the standard grid, the 2D grid will be installed on the detector.

An overview of the 2D grid installation and research CBCT scan process:

1. (See Figure 3). Before the research CBCT scan, the study team will remove the protective cover on the kV x-ray detector and uninstall the standard grid on the detector by removing the screws.
2. They will install the 2D grid on the detector, and a protective cover (as in Picture 1) will be installed over the 2D grid.
3. The process in Steps 1 and 2 will take less than 10 minutes.
4. Subsequently, the study participant will be positioned on the CBCT scanning couch as in his/her radiation treatment position.
5. Study team will leave the room and prepare the standard clinical CBCT scanning protocol that is used for the participant's standard clinical CBCT scans. This way, we will ensure that the same scanning technical parameters will be used for the research and the standard clinical CBCT scan. They will initiate the research CBCT scan. The scan itself will take 1 minute or less. The process in step 5 is expected to take less than 5 minutes.
6. Study team will go back into the room and take the study participant out of the room.
7. After departure of the participant, the study team will acquire one more CBCT scan without the participant. This "blank" scan will be used for system calibration purposes.
8. Study team will download all the CBCT scan raw data of the participant and the calibration scan. They will do the CBCT image reconstruction by using the raw data. This step does not need to be completed immediately. It can be performed hours or days after the research CBCT scan.
9. Study team will uninstall the 2D grid and reinstall the standard grid on the detector. They will perform the calibrations needed to bring the system back to its standard clinical stage. The calibrations performed at this step are part of the standard operating procedures, and they are provided by the CBCT system vendor (e.g. Varian Medical Systems).

It is important to emphasize that research scans described above will not be used during the treatment of the study participant or making clinical decisions. These research CBCT scans will be used solely for research purposes.

6.2 PREPARATION/HANDLING/STORAGE/ACCOUNTABILITY

6.2.1 ACQUISITION AND ACCOUNTABILITY

2D antiscatter grid prototypes will be fabricated by a metal 3D printing manufacturer and will be assembled by PI's team at University Colorado Anschutz Medical Campus. These prototypes will be used throughout the study in all participating institutions. Study investigators will oversee the storage, installation and use of the grid prototypes during research CBCT scans.

6.2.2 FORMULATION, APPEARANCE, PACKAGING, AND LABELING

The 2D grid prototypes will be fabricated from pure tungsten and assembled together using aluminum components. 2D grid will be fabricated using Powder Bed Laser Melting or Direct Metal Laser Sintering additive manufacturing processes. They will be up to 43 cm in width, up to 43 cm in length, and up to 3 cm in height covered with a carbon-fiber or equivalent enclosure.

While the manufacturing process for the 2D grid is different from standard radiographic grids, such as the one used in Varian TrueBeam, materials used in the radiographic grid are similar to the materials in the 2D grid assembly; radiographic grid is composed of lead lamellae separated by fiber spacers. A carbon-fiber or equivalent enclosure is placed around the grid structure.

6.2.3 PRODUCT STORAGE AND STABILITY

2D grid prototypes will be placed in an enclosure while being stored in the locked storage cabinet and during transport from storage to the linac vault to prevent accidental damage to the grids. Grids are kept at room temperature, and they are expected to retain their properties for at least 5 years. The 2D grid and its enclosure do not change form due to x-ray irradiation during CBCT scans.

6.2.4 PREPARATION

Once it is assembled, the 2D grid does not require any preparation for each research CBCT scan.

6.3 MEASURES TO MINIMIZE BIAS: RANDOMIZATION AND BLINDING

Randomization or blinding is not needed during acquisition of CBCT scans of the participants.

In the primary analysis, regions of interest (ROIs) will be placed in CBCT scans by the study team. These regions of interest will be used for calculation of objective image quality metrics. To prevent bias in ROI placement, all CBCT and CT images of a given participant will be coregistered first, such that anatomical locations of ROIs will be comparable in coregistered image sets. Moreover, the locations of ROIs will be cross-checked by a second team member.

6.4 STUDY INTERVENTION COMPLIANCE

- The same immobilization devices, patient position, and scanning protocol will be used for both research and standard clinical CBCT scans. A checklist will be used to assure that the imaging protocol parameters are the same for both research and standard clinical CBCT scans.

- Excessive patient motion during a CBCT scan may degrade image quality and bias the study. The effects of patient motion will be evaluated on a case-by-case basis by the PI. If image quality degradation due to patient motion is deemed excessive, the CBCT scan will be excluded from the study.

6.5 PROHIBITED THERAPY

There are not any prohibited therapies.

6.6 CONCOMITANT THERAPY

There are not any concomitant therapies within this study.

7 STUDY INTERVENTION DISCONTINUATION AND PARTICIPANT DISCONTINUATION/WITHDRAWAL

7.1 DISCONTINUATION OF STUDY INTERVENTION (STOPPING RULES)

The Sponsor-Investigator has the right to terminate this study at any time. Reasons for terminating the study may include, but are not limited to, the following:

- The incidence or severity of adverse events in this or other studies indicates a potential health hazard to patients.
- Patient enrollment is unsatisfactory.

7.2 PARTICIPANT DISCONTINUATION/WITHDRAWAL FROM STUDY

Participants are free to withdraw from participation in the study at any time upon request.

In addition, the investigator has the right to withdraw a patient from the study at any time. Reasons for withdrawal from the study may include, but are not limited to, the following:

- Patient withdrawal of consent at any time
- Any medical condition that the Sponsor-Investigator determines may jeopardize the patient's safety if he or she continues in the study
- Sponsor-Investigator determines it is in the best interest of the patient
- Patient non-compliance with study procedures

Participants must discontinue study intervention if they experience any of the following:

- Any medical condition that may jeopardize patient safety.

Every effort should be made to obtain information on patients who withdraw from the study. The primary reason for withdrawal from the study should be documented on the appropriate eCRF.

8 STUDY ASSESSMENTS AND PROCEDURES

8.1 EFFICACY ASSESSMENTS

The main hypothesis of the study is that 2D antiscatter grid improves tissue visualization and quantitative accuracy in CBCT images. An image quality evaluation study will be performed (described in Section 9). Values of objective image quality metrics extracted from CBCT images will be used to assess tissue visualization.

The efficacy of tissue visualization improvement in research CBCT scans will be assessed with respect to standard clinical CBCT scans.

The efficacy analyses for the secondary objective will be conducted in a similar fashion, and efficacy of study intervention will be assessed with respect to standard clinical CBCT scans.

For the tertiary objective, multiple evaluations will be performed to assess the utility and efficacy of research CBCT scans in different clinical tasks. As this is a pilot study, the PI will determine which clinical tasks will likely benefit from the research CBCT scans acquired in this clinical trial. Some examples of such clinical tasks are: 1) It is hypothesized that clinicians can more consistently delineate anatomy in CBCT images acquired with the 2D grid. An observer study will be conducted to evaluate tissue visualization performance in CBCT images. 2) The consistency of radiomics features in research and standard clinical CBCT scans will be measured and evaluated by using MDCT images of participants as reference, as described in Section 9. MDCT scans will be acquired as part of the standard clinical care of participants. 3) Image quality for target localization tasks will be assessed in a subjective image quality evaluation study, where observers will rank the quality of CBCT images 4) Image quality will be assessed using objective image quality metrics, such as noise, contrast, contrast to noise ratio, and CT number uniformity. 5) CBCT-based dose calculation accuracy by generating treatment plans using CBCT images, and errors in dose volume histogram metrics will be assessed with respect to reference dose in MDCT-based treatment plans. To reiterate, these are example assessments in this exploratory objective, and the PI will determine the specific CBCT-based clinical tasks to be assessed.

8.2 SAFETY AND OTHER ASSESSMENTS

The intervention of this study (one research CBCT scan for photon therapy cohort, and two research CBCT scans for the proton therapy cohort) is not expected to have any detectable effects on study participants, as described in Section 2.3.1. Therefore, evaluation of the participant, such as physical examination or specimen collection and analysis, will not be performed as part of this study.

8.3 ADVERSE EVENTS

8.3.1 DEFINITION OF ADVERSE EVENTS (AE)

Adverse event means any untoward medical occurrence associated with the use of an intervention in humans.
Because this is an imaging study, where no clinical decision will be altered, only AEs that are related to the research intervention or the use of the device will be recorded. The only research procedure is a CBCT scan with the 2D grid attached. In the proton therapy cohort, one more CBCT scan will be acquired without the 2D grid.

As described in Sec. 2.3, we do not anticipate adverse events due to the research intervention itself, such as acute skin reaction due to CBCT imaging dose. However, unforeseen incidents, such as breakdown of the grid during the scan, may occur. Such incidents will be recorded as an AE.

8.3.2 DEFINITION OF UNANTICIPATED ADVERSE DEVICE EFFECTS (UADE)

Unanticipated Adverse Device Effect (UADE) is any serious adverse effect on health or safety or any life-threatening problem or death caused by, or associated with, a device, if that effect, problem, or death, was not previously identified in a nature, severity, or degree of incidence in the investigational plan or application (including a supplementary plan or application), or any other unanticipated serious problem associated with a device that relates to the rights, safety, or welfare of subjects (21 CFR 812.3(s)). This includes any adverse event resulting from insufficiencies or inadequacies in the instructions for use, the deployment, the implantation, the installation, the operation, or any malfunction of the investigational medical device. Additionally, this includes any event that is a result of a use error or intentional misuse.

8.3.3 CLASSIFICATION OF AN ADVERSE EVENT

8.3.3.1 SEVERITY OF EVENT

For AEs not included in the protocol-defined grading system, the following guidelines will be used to describe severity.

- **Mild** – Events require minimal or no treatment and do not interfere with the participant's daily activities.
- **Moderate** – Events result in a low level of inconvenience or concern with the therapeutic measures. Moderate events may cause some interference with functioning.
- **Severe** – Events interrupt a participant's usual daily activity and may require systemic drug therapy or other treatment. Severe events are usually potentially life-threatening or incapacitating.

8.3.3.2 EXPECTEDNESS

Expectedness will only be documented for UADEs. The radiation oncologist will be responsible for determining whether a UADE is expected or unexpected. A UADE will be considered unexpected if the nature, severity, or frequency of the event is not consistent with the risk information previously described for the device.

8.3.4 TIME PERIOD AND FREQUENCY FOR EVENT ASSESSMENT AND FOLLOW-UP

The occurrence of an AE or UADE may come to the attention of study personnel during study visits and interviews of a study participant presenting for medical care, or upon review by a study monitor. All AEs including local and systemic reactions not meeting the criteria for UADEs will be captured on the appropriate CRF. Information to be collected includes event description, time of onset, clinician's assessment of severity, relationship to study product (assessed only by those with the training and authority to make a diagnosis), and time of resolution/stabilization of the event. All AEs related to the study intervention must be documented. All related AEs will be followed to adequate resolution.

Any medical condition that is present at the time that the participant is screened will be considered as baseline and not reported as an AE. UAPs will be recorded in the data collection system throughout the study.

Changes in the severity of an AE will be documented to allow an assessment of the duration of the event at each level of severity to be performed. AEs characterized as intermittent require documentation of onset and duration of each episode.

The PI will record all reportable events with start dates occurring any time after the start of the intervention until the completion of study visit #2. UADEs will be followed until resolution or stabilization. At each study visit, the investigator will inquire about the occurrence of AE/UADEs since the last visit.

8.3.5 ADVERSE EVENT REPORTING

The investigator must record reportable adverse events to the DSMC and IRB according to timetable for reporting specified in sections 8.3.6 and 8.3.7.

8.3.6 UNANTICIPATED ADVERSE DEVICE EFFECTS REPORTING

The Sponsor-Investigator must notify the reviewing IRB and all participating PIs in a UADE safety report of potential serious risks as soon as possible, but in no case later than 10 working days after the Sponsor-Investigator determines that the information qualifies for reporting. The reviewing IRB serves as a proxy to the FDA and will make recommendations whether the UADE should be submitted to the FDA. Thereafter, the Sponsor shall submit such additional reports concerning the effect as the reviewing IRB or FDA requests (21 CFR 812.150(a)(1)).

The Sponsor-Investigator who determines a UADE presents an unreasonable risk to participants shall terminate all investigations or parts of investigations presenting that risk as soon as possible. Termination shall occur not later than 5 working days after the Sponsor makes this determination and not later than 15 working days after the Sponsor first received notice of the effect (21 CFR 812.46(b)(2)).

All UADEs will be followed until satisfactory resolution or until the Sponsor-Investigator or site PI deems the event to be chronic or the adherence to be stable. Other supporting documentation of the event may be requested by the Sponsor-Investigator and should be provided as soon as possible.

All UADEs will be reported using the FDA 3500A Mandatory MedWatch report form unless funding sponsor or drug manufacturer requires use of proprietary form. UADE form can be found at:
http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM048334.pdf

To submit a UADE, email as follows within 24 hours of becoming aware of the event:

To: cem.altunbas@cuanschutz.edu
cpdm.iit@cuanschutz.edu
DSMC@cuanschutz.edu

Subject: 20-1684 UADE Report Form

Attach: FDA 3500A form completed and signed by an Investigator

Follow-up of unresolved unanticipated adverse device effects

Any UADEs that are unresolved at the time of the initial report submission should be followed up by the Investigator for as long as medically indicated, and an updated UADE report submitted at the time new information regarding the event becomes available.

8.3.7 REPORTING OF PREGNANCY

Pregnant patients will not be enrolled in the study. Pregnancy status for female study candidate will be checked via a pregnancy test. A pregnancy test will be given at the treatment simulation (Day 1), which is part of the standard clinical care.

8.4 UNANTICIPATED PROBLEMS

8.4.1 DEFINITION OF UNANTICIPATED PROBLEMS (UAP)

The Office of Human Research Protection (OHRP) considers unanticipated problems involving risks to participants or others to include, in general, any incident, experience, or outcome that meets **all** of the following criteria:

- Unexpected in terms of nature, severity, or frequency given (a) the research procedures that are described in the protocol-related documents, such as the IRB-approved research protocol and informed consent document; and (b) the characteristics of the participant population being studied;
- Related or possibly related to participation in the research ("possibly related" means there is a reasonable possibility that the incident, experience, or outcome may have been caused by the procedures involved in the research); and
- Suggests that the research places participants or others at a greater risk of harm (including physical, psychological, economic, or social harm) than was previously known or recognized.

This study will use the OHRP definition of UAP.

8.4.2 REPORTING OF UNANTICIPATED PROBLEMS

Incidents or events that meet the OHRP criteria for UAPs require the creation and completion of a UAP report. It is the Sponsor-Investigator or Site PI's responsibility to report UAPs to their IRB. The Lead PI is responsible for reporting the UAP to the IRB and the UCCC DSMC. The UAP report will include the following information:

- Protocol-identifying information: protocol title and number, PI's name, and the IRB project number;
- A detailed description of the event, incident, experience, or outcome;
- An explanation of the basis for determining that the event, incident, experience, or outcome represents a UAP;
- A description of any changes to the protocol or other corrective actions that have been taken or are proposed in response to the UAP.

9 STATISTICAL CONSIDERATIONS

9.1 STATISTICAL HYPOTHESES

- Primary Efficacy Endpoint:
  The primary endpoint of this study is to evaluate the change in objective image quality metrics in CBCT images acquired with the 2D grid, when compared to CBCT images without the 2D grid. We will place multiple ROIs in each CBCT scan, and calculate absolute CT number error, artifact amplitude, and contrast to noise ratio (CNR). We will evaluate the statistical significance of the differences of these metrics between research CBCT and standard clinical CBCT scans. We hypothesize that CBCT scan with 2D grid will provide significantly lower CT number errors and artifact amplitudes when compared to standard clinical CBCT scans. We also hypothesize that CBCT scans with 2D grid will provide equivalent or better CNR than standard clinical CBCT scans.

- Secondary Efficacy Endpoint(s):

1) We hypothesize that the accuracy of software tools can also be improved in auto-delineation of tissues in CBCT scans. In this case, we will use manual delineations from the observers as the gold standard and measure the similarity of software generated and observer generated delineations by using the CI and HD metrics.

- Tertiary Efficacy Endpoint(s):

1) Assessment of radiomics feature extraction accuracy: We hypothesize that image intensity and texture (radiomics) features are more consistent in higher quality CBCT images. The gold standard consistency of radiomics features is MDCT scans. Thus, we will evaluate the correlation of radiomics features in CBCT scans and MDCT scans, by using the CCC metric. Higher correlation of radiomics features between CBCT and MDCT scans will yield higher CCC values.
2) Assessment of image quality rankings by observers, evaluation of quantitative image quality metrics, and evaluation of dose calculation accuracy. Metrics obtained in each study will be evaluated comparatively. The statistical significance of differences in quality metrics extracted from research and standard clinical CBCT scans will be evaluated.
3) Determine the consistency of organ/tissue delineations across different observers, when using CBCT image sets with better image quality. We will calculate intra-class correlation coefficient (ICC) on CI and HD metrics to measure the effect of standard clinical CBCT and 2D Grid CBCT on organ delineation consistency.
   We hypothesize that organ/tissue delineations performed by observers will be more accurate, or more consistent, if tissue visualization is better in CBCT scans. However, gold standard tissue delineations do not exist in CBCT scans. Therefore, we will compare the consistency, or similarity, of delineations performed by multiple observers. If tissue visualization is improved in a CBCT scan, we expect higher inter-observer similarity of delineations.

9.2 SAMPLE SIZE DETERMINATION

The sample size calculation is for the primary hypothesis. A total of 32 participants (Groups 1-3) provides non-overlapping 95% confidence intervals to detect an increase of at least 3.5% in the research CBCT ICC compared to a standard CBCT ICC of 0.95. We expect a high-level agreement for the standard CBCT method but if the ICC for the standard CBCT is slightly lower at 0.9 or even 0.8 we are still able to detect an increase in the research CBCT of at least 7.7% and 17%, respectively [34].

9.3 POPULATION FOR ANALYSES

Data from participants who complete both research and standard clinical CBCT scans, and the scans are evaluable, will be used for primary and secondary analyses. The study intervention is a CBCT scan for observation purposes, without any anticipated adverse effects on the participant. Therefore, safety analysis dataset is not needed in this study.

9.4 STATISTICAL ANALYSES

9.4.1 GENERAL APPROACH

Study #1 (Primary objective): Improvement in tissue visualization and quantitative accuracy will be evaluated comparatively between the CBCT scans acquired with and without the 2D grid. Objective image metrics will be employed to quantify tissue visualization and quantitative accuracy. Three image quality metrics will be extracted from each CBCT scan; absolute CT number error, image artifact amplitude, and contrast to noise ratio (CNR). To calculate CT number errors and artifact amplitude, multiple ROIs will be placed primarily in the soft tissue and adipose sections of the imaged anatomy in coregistered CBCT and simulation CT images. CT number error is defined as the absolute difference in mean HU values between the CBCT and the gold standard CT images of a given ROI. Artifact amplitude is defined as the difference between the maximum and minimum value of CT number errors extracted from ROIs in a given CBCT scan. For CNR calculations paired ROIs will be placed in each imaged volume, such that one of the ROIs in the pair will be placed in soft tissue, and the other will be placed in adipose tissue in proximity of the first ROI. CNR is calculated by using the following:

$$CNR = \frac{\left|HU_{soft} - HU_{adipose}\right|}{(\sigma_{soft} + \sigma_{adipose})/2}$$

Where HU_{soft} and $HU_{adipose}$ are the mean HU values of soft tissue and adipose tissue ROI pairs. σ_{soft} and $\sigma_{adipose}$ are the HU standard deviation of soft tissue and adipose tissue ROI pairs. These metrics serve as surrogates that quantify tissue visualization. A statistically significant improvement in these metrics when compared to metrics extracted from standard clinical CBCT scans would indicate that tissue visualization and quantitative accuracy would be potentially improved by CBCT scans with 2D grid.

Study #2 (Secondary Objective), evaluate the consistency of organ delineation by automated software tools: Evaluations in study 2 will be similar as those in study 1. The exception is that the pairwise comparisons will consist of comparing the automated software delineation to delineations for each of the four observers. This will allow us to evaluate how consistent the automated delineation is with human delineations, and whether a given imagining modality results in a more consistent automated delineation.

Study #3 (Exploratory Objective), assess the utility of CBCT images in qualitative and quantitative imaging tasks: Several studies will be considered for the exploratory analysis.

Improvement of organ or anatomical structure visualization by observers: We hypothesize that anatomical structure visualization can be improved by higher quality CBCT images. To quantify tissue visualization, we will ask multiple observers to delineate organ boundaries. Since the ground truth about organ boundaries cannot be determined from images, we will evaluate the inter-observer agreement among delineated structures. Four observers will delineate a set of anatomical

structures in each helical CT and CBCT scan in a blinded fashion. For each image set, a reference delineation will be determined from delineations of four observers using the STAPLE algorithm. Conformity Indexes (CI) and Hausdorff distances (HD) will be used as metrics of similarity. CI is the ratio of the sum of all overlapping volumes between pairs of observers and the sum of all overlapping and all non-overlapping volumes between the same pairs. HD defined as the maximum distance between the closest points of two delineations. CI of one or HD of 0 mm indicates perfect agreement among observers' delineations. We will have CIs and HDs determined between the reference delineation and each observer. This pairwise approach to determine the CIs can be used to account for variability among the observers, which in turn will improve our ability to compare the two imaging modalities.

To evaluate the consistency of organ delineation by different observers, we will calculate intraclass correlation coefficient (ICC), which is a reliability metric. The ICC is simply the proportion of the total variability in the data that can be attributed to variability between participants. In the context of this study, the ICC is directly related to how well the observer delineations agree, with a higher ICC indicating better agreement. Our aim is to evaluate how ICC varies between standard clinical CBCT and CBCT with 2D grid. We hypothesize that the ICC will be better for CBCT with 2D grid.

Analysis of radiomics feature extraction accuracy: In each image set, we will extract series of radiomics features, such as HU value statistics (e.g. mean, variance, and kurtosis), and texture features, such as gray-level co-occurrence matrix, wavelets, local entropy. Accuracy and repeatability of radiomics features in CBCT (both standard and 2D grid CBCT) and gold standard helical CT will be evaluated using Lin's concordance correlation coefficient (CCC) as in Zhao's work [35]. Statistical analysis details of other potential exploratory studies, such as qualitative and quantitative image quality evaluations, and CBCT-based dose calculations will be determined on an ad hoc basis.

The analysis of TrueBeam (Groups 1-3) and Proteus (Group 4) CBCT images. An image quality difference is expected between TrueBeam and Proteus CBCT due to differences in system design (e.g. TrueBeam has bow tie filter, whereas Proteus does not have one), and image reconstruction chain. Therefore, in the primary analysis, we will analyze the data from patient Groups 1-3 (TrueBeam) and Group 4 (Proteus) separately. This way, we will eliminate potential, system-specific image quality bias. In a subgroup analysis, we will investigate the differences in the study results of Groups 2 and 4 (i.e. prostate cancer patients scanned with TrueBeam and Proteus, respectively).

9.4.2 ANALYSIS OF THE PRIMARY EFFICACY ENDPOINT(S)

Our primary analysis will evaluate the tissue visualization and quantitative accuracy of CBCT scans with 2D grid, as measured by objective image quality metrics. These metrics, namely absolute CT number error, artifact amplitude, and CNR, will be extracted from research CBCT

and standard clinical CBCT pairs of each study participant. In each CBCT image set, each metric will be measured from multiple ROIs, and their respective average values will be calculated. Subsequently, these values will be log transformed (natural logarithms) for the validity of normality. The Linear Mixed Effects model will be used to evaluate the differences in image quality metrics among CBCT types, while adjusting the random patients effect. The lower and upper limits of the 95% confidence interval will be calculated for each image quality metric and for each CBCT type. Image quality metrics of research CBCT scans and standard clinical CBCT scans will be compared in a pairwise fashion for the statistical significance of the differences between the two CBCT types. In a subgroup analysis, image quality metrics will be stratified into anatomical region groups and patient size groups to assess the effect of anatomical region and patient size on the image quality differences between the two CBCT types.

9.4.3 ANALYSIS OF THE SECONDARY ENDPOINT(S)

The analysis of this endpoint will be conceptually similar to primary endpoint, but this time, we will evaluate the consistency of delineations performed by automated software tools, which can greatly improve workflow efficiency in CBCT-based treatment monitoring. We will employ Machine Learning-based organ delineation and evaluate its accuracy with respect to observer-delineated structures.

Workflow: 1) Both research and standard clinical CBCT scans will be registered to helical CT images. After registration, observer-delineated structures will be also delineated independently by Machine Learning Methods. 2) Machine Learning based delineations will be compared to observer-generated delineations in CBCT scans. 3) We will use the similarity (i.e. CI and HD) and reliability (i.e. ICC) metrics to assess the consistency between Machine Learning-based and observer-generated delineations. The Machine Learning model for delineation will be selected by the PI, based on the availability of models for anatomical structures delineated by the observer.

9.4.4 SAFETY ANALYSES

This study does not include a formal safety endpoint, and therefore, safety analyses will not be performed.

9.4.5 BASELINE DESCRIPTIVE STATISTICS

The clinical and sociodemographic characteristics of all participants treated will be summarized using descriptive statistics (e.g. means/standard deviations, percentiles, frequencies). Participant characteristics within participant subgroups defined by the site of radiation treatment, the lateral separation groups, and the CBCT system types, will also be generated.

9.4.6 PLANNED INTERIM ANALYSES

There will be no planned interim analyses.

9.4.6.1 SUB-GROUP ANALYSES

1) Subgroup analyses of image quality metrics will be performed for three anatomical site groups:

- Head and Neck
- Pelvis and abdomen
- Prostate or prostate bed

2) A sub-group analysis of image quality metrics will be performed based on the patient size, as measured by the participant's lateral separation in the imaged volume:

- Lateral separation less than 30 cm
- Lateral separation between 30 and 40 cm
- Lateral separation more than 40 cm

3) Participants in the prostate group will be scanned using two substantially different CBCT systems. To investigate the effect of CBCT system on image quality, the following subgroups will be analyzed separately.

- Prostate and prostate bed subgroup scanned with photon therapy CBCT.
- Prostate and prostate bed subgroup scanned with proton therapy CBCT.

For each subgroup, image quality metrics extracted from CBCT scans with 2D grid and standard clinical CBCT scans will be compared in a pairwise fashion. 95% Confidence Intervals for the image quality metrics (primary objective) will be calculated and reported for each of the subgroups. And the pairwise comparisons between subgroups will be conducted by comparing the 95% Confidence Intervals.

9.4.7 EXPLORATORY ANALYSES

The PI will evaluate the feasibility of several potential exploratory analyses methods and proceed with analyses. The following exploratory analyses methods are considered to investigate the utility of improved CBCT image quality. After the completion of research CBCT scans, the PI will consult with the study team to identify the final exploratory analyses methods. Several example exploratory analyses are: 1) We will evaluate the consistency of organ delineation across participants and different observers. We will involve calculating the intra-class correlation coefficient (ICC), a reliability metric, for standard clinical CBCT and research CBCT. The ICC is simply the proportion of the total variability in the data that can be attributed to variability between

participants. In the context of this study, the ICC is directly related to how well the observer delineations agree, with a higher ICC indicating better agreement. For example, an ICC of 0.8 would indicate that 80% of the variance is due to differences between participants, while 20% of the error is due to differences among observers (i.e., within-participant variability) or measurement error. We hypothesize that the agreement among clinicians will be better (i.e., higher ICC) for the research CBCT compared to the standard clinical CBCT. For each patient, the Conformity Index (CI) and Hausdorff distance (HD) will be calculated and used as similarity metrics to calculate and compare ICCs between the imaging modalities as defined below.

For each participant and CBCT modality an average delineation will be determined using the STAPLE algorithm. This average delineation will be used as the reference delineation to compute four pairwise CIs between the reference and each observer. This pairwise approach to determine the CIs was chosen over the generalized conformity index since it can be used to account for variability among the observers, which in turn will improve our ability to compare the two imaging modalities. A two-way random effects model (random effects for participant and observer) will be carried out for each modality to calculate the ICC and its 95% confidence interval using bootstrapping for absolute agreement. The ICC will be calculated using the form ICC(2,k) so that the results can be generalized to any observer with a similar skill set. If the 95% confidence interval of ICC does not overlap between the two modalities, we will conclude they are significantly different at a 0.05 significant level. We will also examine whether anatomical location impacts performance through subgroup analyses on Groups 1-3.

2) The consistency and reproducibility of radiomics features (image texture and intensity features) in CBCT images will be analyzed. Some examples of radiomics features are mean, standard deviation, kurtosis of pixel value histograms, Gray Level Co-occurrence Matrix (GLCM), Gray Tone Difference Matrix (GTDM), and Spatial Correlation of pixel values. Up to 50 prominent radiomics features will be selected using a similar approach as described by Fave et al. [36] and Zhao et al. [35]. Subsequently, correlation of these radiomics features extracted from research and standard clinical CBCT scans will be measured with respect to radiomics features extracted from MDCT scans for all participants and for each subgroup, as listed in Section 9.4.6.1. 2) Qualitative improvement in image quality will be analyzed in an observer study. Standard clinical and research CBCT scans of study participants will be presented to observers in a blind fashion, and observers will rank the quality of images based on their clinical experience. 3) CBCT image quality will be evaluated using quantitative image quality metrics, such as CT number accuracy, contrast to noise ratio, and image noise. The difference in measured image quality metrics between the research and standard clinical CBCT scans will be evaluated. 4) Radiotherapy dose calculations will be performed by using standard clinical and research CBCT scans. Dose calculated with CBCT scans will be compared to the dose calculated with the gold standard MDCT scans by using dose volume histogram metrics. Dosimetric differences between each CBCT-MDCT dose pair will be analyzed. We hypothesize that dose calculated with research CBCT scans will have lower dosimetric errors than the dose calculated with standard clinical CBCT scans.

10 SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

10.1 REGULATORY, ETHICAL, AND STUDY OVERSIGHT CONSIDERATIONS

10.1.1 INFORMED CONSENT PROCESS

10.1.1.1 CONSENT/ASSENT AND OTHER INFORMATIONAL DOCUMENTS PROVIDED TO PARTICIPANTS

Consent forms describing in detail the study intervention, study procedures, and risks are given to the participant and written documentation of informed consent is required prior to starting intervention/administering study product.

10.1.1.2 CONSENT PROCEDURES AND DOCUMENTATION

Informed consent process will be initiated prior to the individual's agreeing to participate in the study and continues throughout the individual's study participation. Extensive discussion of the risks and possible benefits of participation will be provided to the participants and their families.

Consent forms will be IRB-approved, and the participant will be asked to read and review the document. The investigator will explain the research study to the participant and answer any questions that may arise. All participants will receive a verbal explanation in terms suited to their comprehension of the purposes, procedures, and potential risks of the study and of their rights as research participants. Participants will have the opportunity to carefully review the written consent form and ask questions prior to signing. The participants will have the opportunity to discuss the study with their surrogates or think about it prior to agreeing to participate. The participant will sign the informed consent document prior to any procedures being done specifically for the study.

The participants may withdraw consent at any time throughout the course of the trial. A copy of the informed consent document will be given to the participants for their records. The rights and welfare of the participants will be protected by emphasizing to them that the quality of their medical care will not be adversely affected if they decline to participate in this study.

The study allows the inclusion of non-English speaking and non-reading participants. Witnesses to these consent processes will be individuals not associated with the trial and will not have a conflict of interest.

10.1.2 STUDY DISCONTINUATION AND CLOSURE

This study may be temporarily suspended or prematurely terminated if there is sufficient reasonable cause. Written notification, documenting the reason for study suspension or termination, will be provided by the suspending or terminating party to Sponsor-Investigator. If the study is prematurely terminated or suspended, the Sponsor-Investigator will promptly inform the IRB and will provide the reason(s) for the termination or suspension.

Circumstances that may warrant termination or suspension include, but are not limited to:

- Determination of unexpected, significant, or unacceptable risk to participants.
- Demonstration of efficacy that would warrant stopping.
- Insufficient compliance to protocol requirements.
- Data that are not sufficiently complete and/or evaluable.
- Determination of futility.

Study may resume once concerns about safety, protocol compliance, and data quality are addressed and satisfy the Sponsor, IRB, DSMC, and/or FDA.

10.1.3 CONFIDENTIALITY AND PRIVACY

Participant confidentiality is strictly held in trust by the participating investigators, their staff, and the Sponsor-Investigator(s) and their agents. This confidentiality is extended to the clinical information relating to participants. Therefore, the study protocol, documentation, data, and all other information generated will be held in strict confidence. No information concerning the study or the data will be released to any unauthorized third party without prior written approval of the sponsor.

The study Monitor, other authorized representatives of the Sponsor-Investigator, representatives of the IRB, or pharmaceutical company supplying study product may inspect all documents and records required to be maintained by the investigator, including but not limited to, medical records (office, clinic, or hospital) and pharmacy records for the participants in this study. The clinical study site will permit access to such records.

The study participant's contact information will be securely stored at each clinical site for internal use during the study. At the end of the study, all records will continue to be kept in a secure location for as long a period as dictated by local IRB and Institutional regulations.

Study participant research data, which is for purposes of statistical analysis and scientific reporting, will be transmitted to and stored at the University of Colorado Cancer Center. This will not include the participant's contact or identifying information. Rather, individual participants and their

research data will be identified by a unique study identification number. The study data entry and study management systems used by clinical sites and by the University of Colorado Cancer Center research staff will be secured and password protected. At the end of the study, all study databases will be de-identified and archived at the University of Colorado Cancer Center.

10.1.4 FUTURE USE OF STORED DATA

- **Intended Use:** Data collected under this protocol may be used to study the tissue visualization and quantitative accuracy of CBCT images. No genetic testing will be performed.
- **Storage:** Data will be stored using codes assigned by the investigators. Data will be kept in password-protected computers. Only Investigators will have access to the data. Clinical data will be entered into REDCap. The data system includes password protection and internal quality checks, such as automatic range checks, to identify data that appear inconsistent, incomplete, or inaccurate.
- **Tracking:** Data will be tracked using a password-protected spreadsheet.
- **Disposition at completion of the study**: Study participants who request destruction of data will be notified of compliance with such request and all supporting details will be maintained for tracking.

Data collected for this study will be analyzed and stored at the University of Colorado Cancer Center. After the study is completed, the de-identified, archived data will be transmitted to and stored at in data servers at the University of Colorado Cancer Center under the supervision of lead PI for use by other researchers including those outside of the study. Permission to transmit data to the University of Colorado Cancer Center and to other researchers will be included in the informed consent.

During the conduct of the study, an individual participant can choose to withdraw consent to have data stored for future research.

When the study is completed, access to study data will be provided through the University of Colorado Cancer Center.

10.1.5 SAFETY OVERSIGHT

The Sponsor-Investigator will be responsible for monitoring the trial per the trial monitoring plan, in addition to overseeing the safety and efficacy of the trial including any specimens collected, executing the data and safety monitoring (DSM) plan, and complying with all reporting

requirements to local and federal authorities. This oversight will be accomplished through additional oversight from the Data and Safety Monitoring Committee (DSMC) at the University of Colorado Cancer Center (CU Cancer Center). The DSMC is responsible for ensuring data quality and study participant safety for all clinical studies at the CU Cancer Center, which is the coordinating institution of this trial. A summary of the DSMC's activities is as follows:

- Conduct of internal audits
- Ongoing review of all unanticipated adverse device effects (UADEs), serious adverse events (SAEs), and unanticipated problems (UAPs)
- May submit recommendations for corrective actions to the CU Cancer Center's Executive Committee

Per the CU Cancer Center Institutional DSM Plan, SAEs and UAPs are reported to the DSMC, IRB and the Sponsor_Investigator per protocol. All SAEs and UAPs including unanticipated adverse device effects are to be reported to the DSMC within 7 (for fatal or life-threatening events) or 15 (non-life-threatening events) calendar days of the sponsor investigator receiving notification of the occurrence.

Each participant's treatment outcomes will be discussed by the PI and site PI and appropriate staff at regularly scheduled meetings. Data regarding the number of participants, adverse device effects, treatment modifications and treatment responses will be discussed and documented in the meeting's minutes.

The Sponsor-Investigator is responsible for organizing and conducting regularly scheduled teleconferences with all participating sites. The Sponsor-Investigator will also be responsible for including data from all of the participating sites to include the minutes from these regularly scheduled teleconferences between the Sponsor-Investigator and the sites within the overall trial's DSM progress report.

The Sponsor-Investigator will provide a DSM progress report to the CU Cancer Center DSMC on a recurring basis (either every six or twelve months based on DSMC vote). The DSM report will include a protocol summary, current enrollment numbers, summary of adverse device effects to include specific unanticipated adverse device effects, SAEs, UAPs and AEs, any treatment modifications, all protocol deviations, and protocol amendments. The DSM progress report submitted to the DSMC will also include, if applicable, the results of any efficacy data analysis conducted. Results and recommendations from the review of this progress report by the DSMC will then be provided to the Sponsor-Investigator in a DSMC review letter. The Sponsor-Investigator is then responsible for ensuring this letter is submitted to the site's IRB of record at the time of IRB continuing review.

10.1.6 CLINICAL MONITORING

Clinical site monitoring will be conducted to ensure that the rights and well-being of human participants are protected, that the reported trial data are accurate, complete, and verifiable, and that the conduct of the trial is in compliance with the currently approved protocol/ amendment(s), with GCP, and with applicable regulatory requirement(s).

Monitoring for this study will be performed by a CU Cancer Center Clinical Monitor in accordance with the clinical monitoring plan (CMP), incorporated herein by reference. The CMP describes in detail who will conduct the monitoring, at what frequency monitoring will be done, at what level of detail monitoring will be performed, and the distribution of the monitoring reports.

10.1.7 QUALITY ASSURANCE AND QUALITY CONTROL

Quality Control (QC) procedures will be implemented beginning with the data entry system and data QC checks that will be run on the database will be generated. Any missing data or data anomalies will be communicated to the site(s) for clarification/resolution.

Following written SOPs, the study Monitor will verify that the clinical trial is conducted, and data are generated, documented (recorded), and reported in compliance with the protocol, GCP, and the applicable regulatory requirements [e.g., Good Laboratory Practices (GLP), Good Manufacturing Practices (GMP)].

The investigational site will provide direct access to all trial-related sites, source data/ documents, and reports for the purpose of monitoring and auditing by the DSMC audit team, and inspection by local and regulatory authorities.

10.1.8 DATA HANDLING AND RECORD KEEPING

10.1.8.1 DATA COLLECTION AND MANAGEMENT RESPONSIBILITIES

Data collection is the responsibility of the clinical trial staff at the site under the supervision of the site PI. The PI is responsible for ensuring the accuracy, completeness, legibility, and timeliness of the data reported.

All source documents should be completed in a neat, legible manner to ensure accurate interpretation of data. When making changes or corrections, cross out the original entry with a single line, and initial and date the change. DO NOT ERASE, OVERWRITE, OR USE CORRECTION FLUID OR TAPE ON THE ORIGINAL.

Copies of the electronic CRF (eCRF) will be provided for use as source documents and maintained for recording data for each participant enrolled in the study. Data reported in the eCRF derived from source documents should be consistent with the source documents or the discrepancies should be explained and captured in a progress note and maintained in the participant's official electronic study record.

Clinical data (including reportable AEs) will be entered into a data capture system provided by the University of Colorado Cancer Center. The data system includes password protection and internal quality checks, such as automatic range checks, to identify data that appear inconsistent, incomplete, or inaccurate. Clinical data will be entered directly from the source documents.

10.1.8.2 STUDY RECORDS RETENTION

Study documents should be retained for a minimum of 2 years after the last approval of an investigational marketing application and until there are no pending or contemplated marketing applications or until at least 2 years have elapsed since the formal discontinuation of clinical development of the investigational product. These documents should be retained for a longer period, however, if required by local regulations or institutional policies. No records will be destroyed without the written consent of the Sponsor, if applicable. It is the responsibility of the Sponsor to inform the PI when these documents no longer need to be retained.

10.1.9 PROTOCOL DEVIATIONS

A protocol deviation is any noncompliance with the clinical trial protocol, GCP, or SOP requirements. The noncompliance may be either on the part of the participant, the Investigator, or the study site staff. As a result of deviations, corrective actions are to be developed by the site and implemented promptly. These practices are consistent with ICH E6, sections:

- 4.5 Compliance with Protocol, sections 4.5.1, 4.5.2, and 4.5.3.
- 5.1 Quality Assurance and Quality Control, section 5.1.1.
- 5.20 Noncompliance, sections 5.20.1 and 5.20.2.

It is the responsibility of the study team to use continuous vigilance to identify and report deviations. All deviations must be addressed in study source documents, reported to DSMC, COMIRB, and NCI. Protocol deviations must be sent to the local IRB per institutional guidelines. The site PI/ study staff is responsible for knowing and adhering to their IRB requirements. Further details about the handling of protocol deviations will be included in the -SOP and/or study procedures manual.

10.1.10 PUBLICATION AND DATA SHARING POLICY

This study will ensure that the public has access to the published results of this research.

As required, either for publication (the ICMJE or other publication policy), or according to U.S. regulations (Section 801 of the Food and Drug Administration Amendments Act of 2007) this clinical trial will be registered in a public trials registry including ClinicalTrials.gov, which is sponsored by the National Library of Medicine, and the NCI CTRP Registry for cancer clinical trials.

10.1.11 CONFLICT OF INTEREST POLICY

Independence of this study from any actual or perceived influence, such as by the pharmaceutical industry, is critical. Any actual conflict of interest of persons who have a role in the design, conduct, analysis, publication, or any aspect of this trial will be disclosed and managed.by the University of Colorado Denver's (UCD) Office of Regulatory Compliance Conflict of Interest and Commitment Management (COIC) program. Persons with a perceived conflict of interest will have such conflicts managed in a way that is appropriate to their participation in the trial. Conflict of Interest management plans are project-specific and are reviewed at least annually. UCD has integrated the institutional conflict of interest management program with its existing program.

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